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A MONTHLY DEVOTED TO THE
DISEASES OF INFANTS AND CHILDREN

JOHN FITCH LANDON, M.D., Editor

LEADING ARTICLES IN THIS NUMBER

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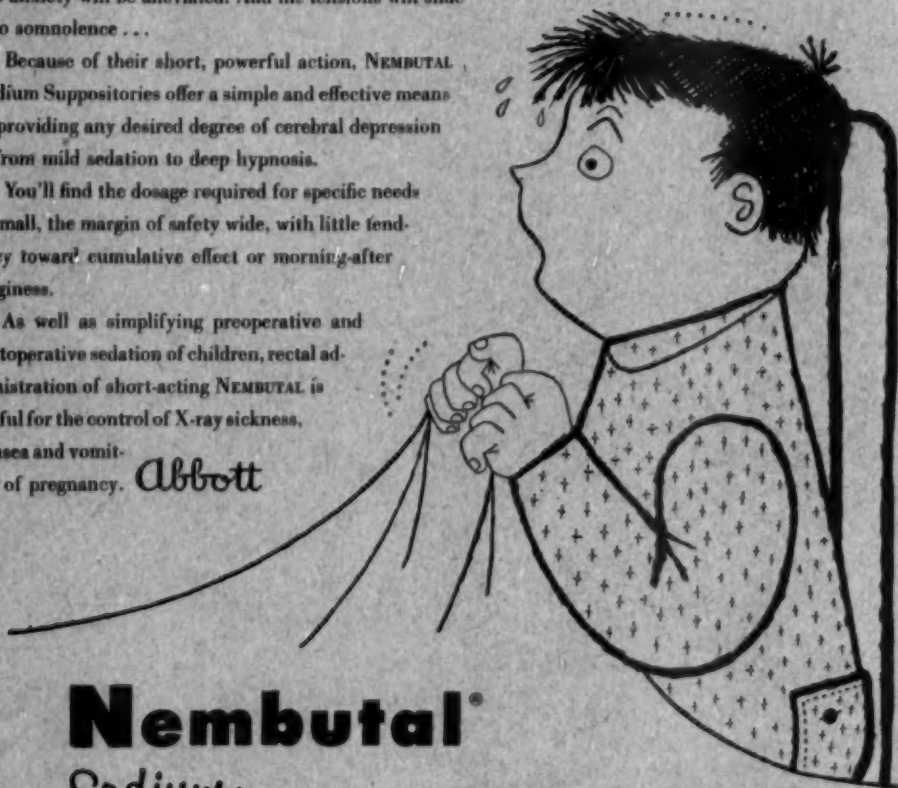
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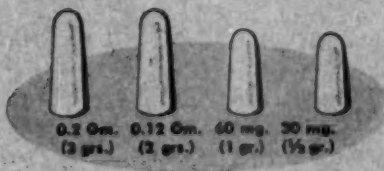


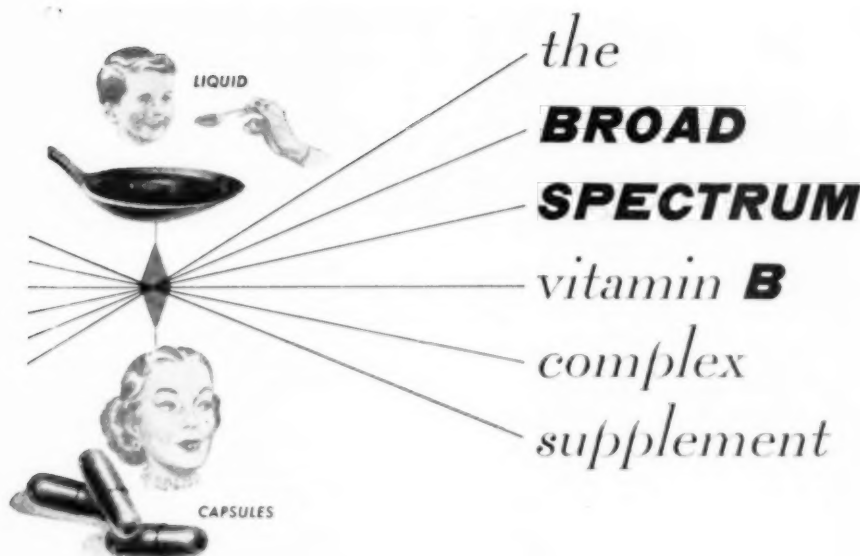
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THE TRUTH ABOUT FROZEN ORANGE JUICE

Significant Dietary Advantages Of Fresh-Frozen Minute Maid Orange Juice Over Home-Squeezed Orange Juice Shown By Independent Research

RECENT assays¹ emphasize the nutritional superiority of reconstituted Minute Maid Fresh-Frozen Orange Juice over home-squeezed orange juice in three important respects:

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from tree to table. Controlled laboratory tests have shown an average ascorbic acid loss of 10.7% in whole oranges after 11 days under simulated storage and shipping conditions.

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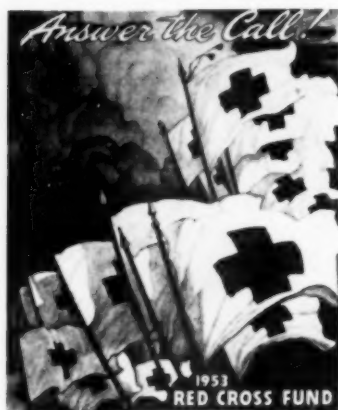
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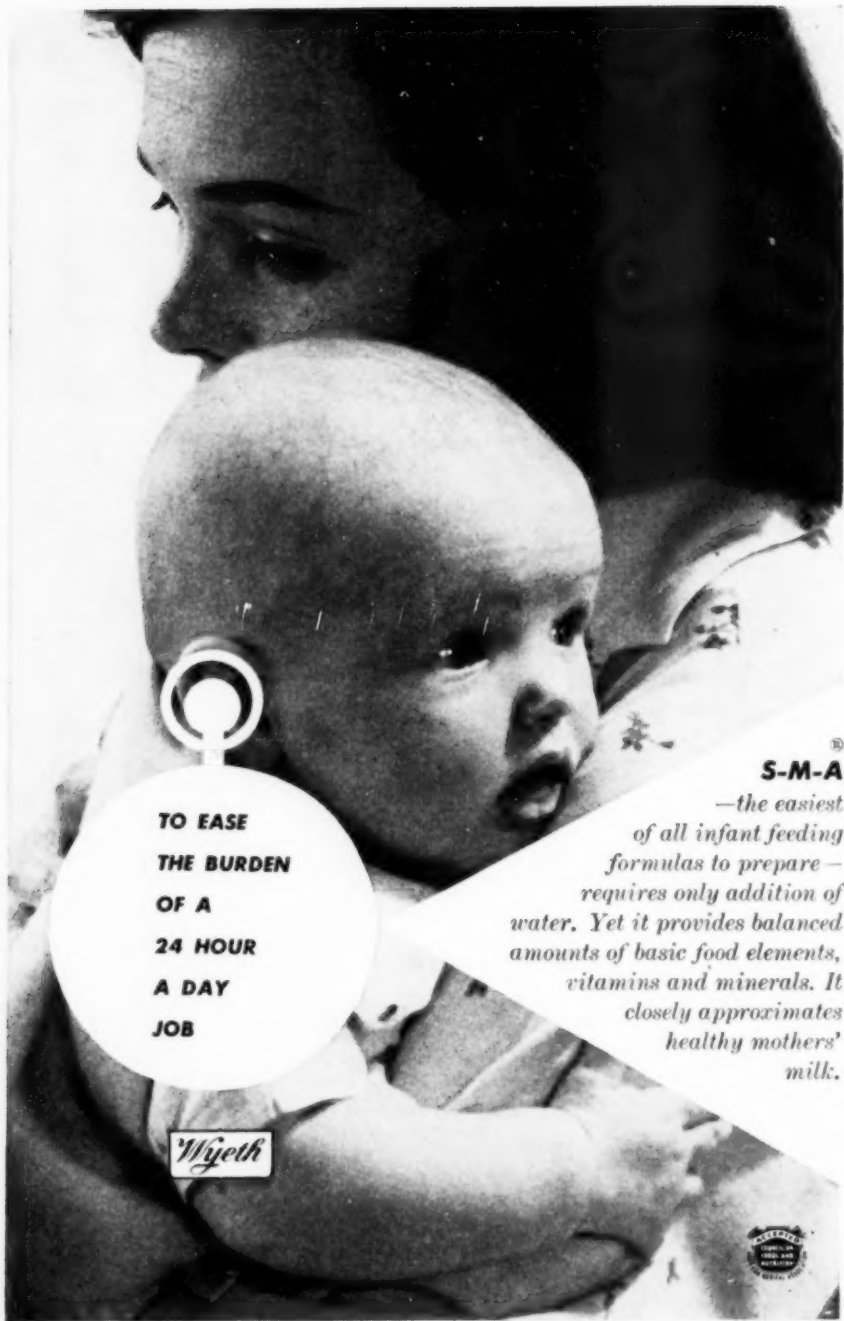
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THE SIGNIFICANCE OF VIREMIA IN THE PATHWAY OF INFECTION OF POLIOMYELITIS

YOSHITO NISHIZAWA, M.D.

AND

KINYA OKANO, M.D.

Osaka, Japan.

Differing from many bacterial diseases there are yet many points that have not been cleared as to the pathogenesis and pathognosis of virus diseases, but these are gradually being clarified with progress in the study of medicine. From this viewpoint, poliomyelitis is also in this category and it is needless to state that many new concepts are being developed as to its interpretation.

The history of research on this disease in Japan is short and only the outstanding studies by the late Professor Kasahara^{1,2} are found. Since then Nishizawa^{3,4}, one of the authors, has developed the glutamylcholine treatment in the field of therapeutics. On the other hand, we have been carrying out studies on the infectious pathway of this disease based on pathological-anatomical observations in the human body⁵. The conclusion was drawn that this is a generalized systemic disease coming as a result of viremia from patho-histological findings in monkeys and in mice experimentally infected with the virus and from studies in which the virus was isolated from the blood^{6,7}. The composite results are reported here.

The theory of gastro-intestinal portal of entry in regards to the infectious pathway is gaining favor due to recent studies⁷, so that its pathological verification has become necessary. The old report by

Professor of Pediatrics, School of Medicine, Osaka University (Dr. Nishizawa).

Peabody⁸ is found in regard to this point but it is believed that a systematic, accurate report is yet to be compiled. Next the questions of invasion and multiplication of the virus in the body are the most hotly debated points. The theory of strict neurotropism which had been most widely accepted is gradually losing strength with the successful cultivation of the virus recently in extra-neural tissue media by Ledinko⁹, Enders¹⁰ and others. It would naturally be necessary to confirm this by observations on morphological changes in the various organs in poliomyelitis cases. The focal point of our conclusion stated above would then become apparent.

Of the previous studies concerning changes in extra-neural tissue, there are reports by Peabody on lymphatic tissue, Wenner¹¹ and Anbo¹² on interstitial pneumonia and Stechle¹³ on hepatitis. Dolgop¹⁴ has studied pathological changes in the cardiac muscle and Denst¹⁵ in the peripheral muscles, but all of these reports are fragmentary and there is nothing suggesting overall changes due to viremia, much less any scientific theories substantiated by experimental data.

By chance, the very recent hypothesis by Bodian¹⁶ regarding viremia was identical with the theory advanced by us just one month previously. This was very interesting indeed. However, if the points of difference are raised here, our conclusions were based on autopsy findings, histological findings, following experimental infection and isolation of the virus from the blood while their work was based merely on the reisolation of the virus from the blood. Furthermore we believe that the pathway by which the virus reaches the central nervous system is the choroid plexus.

The findings in this study will be taken up in the following order:

(I) Pathological observation at autopsy of 10 cases of poliomyelitis and the hypothesis attained from these observations.

(II) Experimental data derived from studies in which monkeys and mice were experimentally infected with the Lansing virus to verify the hypothesis attained in (I).

(III) Summarization of (I) and (II) formulating the theory.

I. AUTOPSY FINDINGS

A. *Weight of the Organs.* The weight of the various organs was compared to that of the average Japanese of the same age

(Sato¹⁷) and showed the most clear-cut increase in weight was in the brain and a marked difference was noted in all cases. Even macroscopically, inflammatory edema and hyperemia of the cerebral parenchyma could be seen. An increase in weight of the kidney was noted in 7 out of 8 cases and microscopically, hyperemia and cloudy swelling is apparent. A definite though not general increase in weight could also be seen in the other organs and corresponding inflammatory findings are present.

B. *Changes in the Central Nervous System.* The central gyrus of the cerebrum, the nucleus lentis, the area surrounding the aqueduct, the pons, the vermix of the cerebellum, the bulbous of the medulla, the cervical, thoracic and lumbar cords were examined. Exact examinations were carried out following staining with Weigert-Paul myelin sheath stain, Bielschowsky's axis stain, Sudan III fat stain, Nissl's stain and hematoxylin eosin.

It can conclusively be said that changes are found in all of the above sites and it is believed that the strongest effects are found in the nuclei (in the broad sense) in the area neighboring the ventricles. The picture of more extensive changes in the motor centers of the cortex compared to the sensory centers mentioned by Bodian¹⁷ was not noted.

Vascular changes and the degree of degeneration of the nerve cells were approximately parallel in the various sites, but not always so, and in accordance with Hurst et al.¹⁸ we cannot agree with the suggestion of Benecke²⁰ that vascular changes give rise to degeneration of the nerve cells.

C. *General Systemic Vascular and Interstitial Tissue Reaction* (believed to be due to viremic change). As stated above, studies had already been carried out regarding generalized systemic tissue reactions in anticipation of viremia. Interstitial hepatitis was seen in 9 out of 10 cases and round cell infiltration could be seen in the lobules and Glisson sheath (Fig. 1). Furthermore, fatty degeneration of the liver parenchymal cells was characteristic, with central degeneration in five, diffuse in four and peripheral degeneration in one case (Fig. 2).

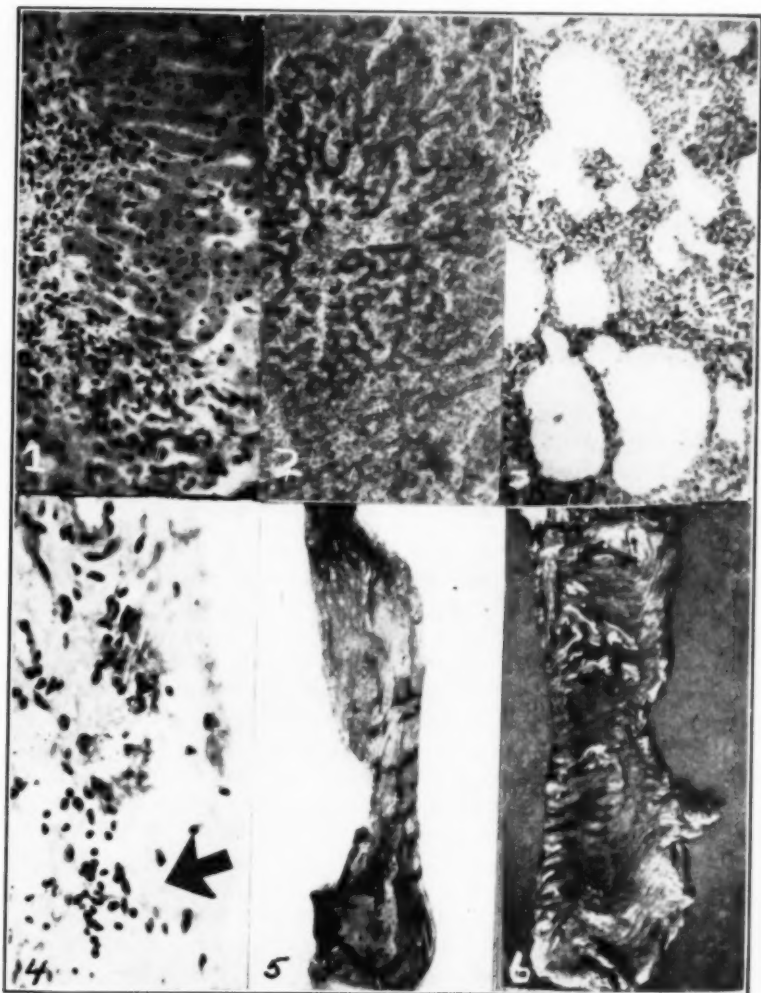
Liver dysfunction can naturally be expected, and when the liver function was tested clinically, it was found that the Millon and histidine reactions reach a high percentage (72 per cent) during the second week after onset.

The lung is markedly hyperemic and swollen macroscopically and a picture suggesting a combination of pneumonia and emphysema could be seen in many cases. Microscopically, round cell infiltration and hyperemia of the interstitial tissues could be seen in most cases though differing in degree. Findings suggesting interstitial pneumonia were noted and this was particularly noticeable in case number 95 where there was a marked change in the intestinal tract. Other forms of pneumonia were also noted (Fig. 3).

In the other organs, too, as the heart, pancreas, etc., hyperemia, marked round cell infiltration, swelling, etc., could be seen (Fig. 4).

To summarize the findings: characteristic changes inherent to viral infections as vascular hyperemia and round cell infiltration of the surrounding tissue can be seen in this disease and these findings are also present in the various organs outside of the central nervous system. Furthermore, edema and parenchymal degeneration are also found. As these changes are also found in the monkeys experimentally infected, it is believed that it is not unreasonable to suggest that these histological findings are characteristic viremic vascular interstitial reactions of poliomyelitis.

D. Changes in the Intestinal Tract and Lymphatic Tissues. Many studies have been recently published supporting the theory of gastro-intestinal infection. However, no statistical, classified observations of the macroscopic findings have been reported so studies were carried out by careful observations of the findings from the viewpoint of a viral enteritis. The greatest changes were found in the region between the terminal end of the ileum and 50 cms. or more proximal to it. (Differs with age.) The changes consist of hyperemia, hemorrhage and necrotic degeneration at intervals of about 10 cms. coinciding with the Peyer's plaques and a diffuse striped hyperemia coinciding with the intestinal folds. Also catarrhal changes were noted (Fig. 5 and 6). Histologically, not only simple hyperemia and hemorrhage are present in the submucosa but, in typical cases, round cell and histiocyte infiltration can be seen in the tissues surrounding the blood vessels. It is believed that this is a type of viral enteritis. Nuclear destruction and enlargement of the cells of the germinal center of the lymphatic apparatus of the intestines and proliferation and enlargement of the endothelial cells of the blood vessels are marked.



(1) Interstitial hepatitis (human). Interacinar round cell infiltration. Hematoxylin and eosin stain. X400. (2) Fatty degeneration of the liver (human). Sudan III stain. X100. (3) Interstitial pneumonia (human). Hematoxylin and eosin stain. X150. (4) Pericarditis (human). Arrow points to round cell infiltration. Hematoxylin and eosin stain. X400. (5) Terminal ileitis (human). Hyperemia and hemorrhage. (6) Acute colitis of the colon ascendens (human).

Hyperemia and enlargement of the regional lymph nodes parallels changes in the intestinal tract and in the more pronounced cases, hemorrhage can be seen. Microscopically, hemosiderin cells and wandering cells can be seen besides the above findings, and in many places findings resembling the so-called Hellman's reaction center are noted.

The omental lymph nodes are hyperemic and moderately enlarged and, in severe cases, there are massive peritoneal adhesions around the site of change in the intestine. The inguinal lymph nodes are also distinctly hyperemic and swollen as are the mesenteric nodes in cases in which the changes in the intestine are severe.

In the spleen, destruction of the nuclei, hyalinization, effusion, hyperemia and other signs of inflammation can be seen in the follicular centers.

Enlargement and degeneration of the reticulo-endothelial cells and hyperemia can be seen in the thymus.

II. EXPERIMENTAL INFECTION STUDIES

Studies in experimental infection were carried out by giving the Lansing strain virus orally, intravenously and intracerebrally to monkeys and by the oral and intravenous (caudal vein) routes to mice.

A. Pathological Findings. 1. *Intracerebrally Inoculated Monkeys:* It is needless to say that the histological changes in the brain and spinal cord consisted of degeneration of the nerve cells, vascular reactions, such as, round cell infiltration and hyperemia. Aside from these, interstitial changes were also observed in the liver, lungs, pancreas, kidney and heart. Fatty degeneration of the liver, degeneration centering in the follicle of the spleen, were noted also. In other words, the same general changes seen in the human could be seen here.

2. *Orally Infected Monkeys:* This group was inoculated by feeding 20.0 cc. of 7-10 per cent Lansing virus suspension by means of a stomach tube over a period of 1-3 days. The animals were sacrificed after 6-16 days and examined. The mucosa of the intestines showed a slight hyperemia and catarrhal changes. Microscopically, distinct changes, such as, small hemorrhages, neuronophagia, satellitosis, etc., could be seen in the anterior horn of the

spinal cord. Other findings, as interstitial hepatitis, fatty liver and interstitial pneumonia, corresponded with those observed in the intracerebrally inoculated group and in humans.

3. Intravenously Inoculated Monkeys: 10.0 cc. of 7 per cent Lansing virus suspension was inoculated intravenously in this group and the animals sacrificed after 4 days. Hemorrhages and changes in the nerve cells were observed in the spinal cord as in (2). Hemorrhages and hyperemia were found in the lungs.

B. *Virus Re-isolation Experiments.* Venous blood was drawn every day from the monkeys inoculated by means of the gastric tube. This blood was defibrinated and 0.03-0.05 cc. of the whole blood was inoculated intracerebrally into white mice. Virus was successfully re-isolated from the blood in two cases. In the first case, the blood was obtained on the 6th day after inoculation and, in the second, the blood was of the 6th and 7th days.

C. *Studies on the Transfer of Fuchsin to the Spinal Fluid and Changes in the Structure of the Epithelium of the Choroid Plexus.* 2.0 cc. per Kgm of 10 per cent acid fuchsin was injected intravenously in monkeys and, after 30 minutes, 1.0 cc. of spinal fluid was removed for examination. The fuchsin content of the spinal fluid was measured by means of the Duboscq's colorimeter. It was found that compared to the normal, 8.8 times more fuchsin was transferred to the spinal fluid in the orally inoculated monkeys and 3.6 times more in the intravenously inoculated monkeys.

The choroid plexus was then examined. After fixing in Luna's solution and Levi's solution, the material was stained with Heidenhain's iron hematoxylin. Examination of the vacuole formation, the number and form of the mitochondria of the epithelial cells of the choroid plexus showed a picture of increased secretory function. It is believed that this is a sign that the virus in the blood enters the central nervous system through the choroid plexus.

D. *Experimental Infection by Intravenous Inoculation in Reticulo-endothelial System Blocked Mice.* The reticulo-endothelial system was blocked by repeated injection of india ink in mice approximately 14 gms. in weight. 0.05 cc. of 10 per cent Lansing virus suspension was then injected into the caudal vein. At the same time, an identical amount was injected in the same way into normal controls. Of the blocked group, 2 out of 17 became infected. Histo-pathological examination of these showed the same

changes as in intracerebrally injected mice. No infection was seen in the control group.

DISCUSSION

In formulating a theory, it is necessary to first observe the facts and then to prove the hypothesis built on these facts through model experiments. It is only then that this theory becomes inherent. We applied this process to the study of poliomyelitis. Clinical and pathological findings, animal experiments and autopsy findings were investigated and the results were as stated above. In summarizing the above findings it is suggested that as was reported by Nishizawa at the meeting of the Japan Infectious Diseases Society, viremia occurs early in the course of the disease. This viremia results from entry by way of the intestines. Then multiplication takes place in the extra-neural tissues. The virus then invades the central nervous system via the choroid plexus and is excreted from the intestinal tract. This is almost identical with the scheme advanced by Bodian but it differs in that they based their hypothesis on the re-isolation of the virus from the blood alone. Our theory is based on the histological reactions, re-isolation of the virus from the blood and the hypothesis that the virus passes through the choroid plexus. The findings in the intestines also point morphologically toward the theory of intestinal infection and when their site of preference, degree, condition and relationship to the central nervous system and other organs is studied carefully, it is believed that they substantiate further our previous reports.

It is said that in carrying out medical investigations on diseases, not only the inductive method of statistically observing a large number of cases and consolidating data is accepted but an exact conclusion can be reached even though the number of cases is small if typical changes of a high degree are found. We would like to emphasize that we not only observed a large number of cases with changes in the intestinal tract but very marked changes, as seen in case number 95, were also found.

It is believed that the fact that the weight of the brain was increased in general should be investigated further.

CONCLUSIONS

The following results were obtained from experimental studies

on five monkeys and on white mice and from anatomical studies in 10 cases of Landry's type of poliomyelitis.

1. In examining the weight of the various organs in the human cases, it was found that in almost all of the cases the brain was markedly heavier compared to that of the normal Japanese of the same age. The kidney was heavier in 7 out of 8 cases and, in other organs too, an increase in weight was noted.

2. Round cell infiltration, hyperemia and other signs of interstitial, exudative and proliferative inflammation of the blood vessels were found not only in the central nervous system of both human and experimental animals but also in the liver, lungs, kidney, pancreas, heart, etc. Besides these findings, degeneration of the parenchymal cells could be seen in the liver (fatty liver), heart, lymph nodes and spleen. It is believed from a general viewpoint that these findings are due to a generalized systemic reaction to viremic inflammation.

3. Lansing virus was successfully re-isolated from the blood of orally inoculated monkeys. In one case, the blood was obtained on the 6th day after gastric inoculation and, in the second, the blood was obtained on the 5th and 7th days.

4. Two out of seventeen mice became infected following intravenous inoculation through the caudal vein after the reticulo-endothelial system had been blocked with india ink.

5. The transfer of acid fuchsin injected intravenously to the spinal fluid was increased in both orally and intravenously inoculated monkeys. A picture of increased secretory function was also noted in the epithelium of the choroid plexus.

6. The positive reaction of the Millon and histidine tests, which were used clinically to test liver function in poliomyelitis patients, was highest (70 per cent) two weeks after onset.

7. In summarizing the above, it has been shown that in this disease there is a general systemic infection. This was derived from the observation of viremia in all the organs, and its experimental verification and the theory of viremic, histological reaction is advanced here. It is also believed that pathognostic findings of intestinal infection have been successfully shown.

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CONGENITAL PYLORIC STENOSIS: RESULTS OF OPERATIVE TREATMENT IN 102 CASES. (Ugeskrift for Læger, Copenhagen, 114: 37, Jan. 10, 1952). Vesterdal finds that surgical treatment of pyloric stenosis is more advantageous than medical treatment. Among 90 boys and 12 girls, aged 15 days to 4 months, treated operatively in the period from 1947 to 1950, there were no post-operative deaths. The average duration of hospitalization was 15 days. In one case reoperation was necessary because of adhesions at the site of the pyloric incision. Follow-up from four months to four years after discharge revealed two deaths, neither one attributable to the pylorotomy. In 84 cases the course has been uncomplicated, in 11 there had been slight vomiting for a time, in 3 cases the infants had not thrived at first, and in 2 instances there had been prolonged catarrhal disorder and dyspepsia. The importance of adequate preoperative treatment of dehydration for good results is stressed.—*Journal A.M.A.*

A PROVEN CASE OF A CURED DISSEMINATED COCCIDIOIDOMYCOSIS*

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There are no reported absolutely proven cases of cured disseminated coccidioidomycosis mentioned in the current literature or textbooks. The following case is reported because of this fact and to also show that a systemic fungus infection of coccidioidal etiology can be entirely cured when in the severely disseminated state.

CASE REPORT

A four-year-old Mexican boy was admitted to the pediatric service of the Kern General Hospital March 30, 1952 because, for the past thirty days, he had become blind, and had pain in his right thigh and could not walk.

The past history revealed that he was born in the Kern General Hospital, August 16, 1947. He weighed 8 pounds 13 ounces. He was a first born and breast-fed for two months. He had contracted measles complicated by bronchopneumonia at 7 months of age. He was admitted to the hospital March 29, 1948 and was signed out by parents March 30, 1948. An x-ray confirmed the diagnosis of bronchopneumonia. A routine coccidioidin and Mantoux skin tests were done but the patient left before the time to read them.

Child was readmitted June 28, 1948 with a history of a sudden onset of grunting respiration. The family history was negative for tuberculosis, diabetes or allergy. The father was a farm laborer. The environmental history revealed that three people lived in one room and without refrigeration but had an outhouse. The child's diagnosis was changed to pulmonary primary coccidioides, as a 2 plus coccidioidin skin test was obtained. The hemoglobin was 10.5 grams and 68 per cent. The urine was essentially negative. The patient was then 10 months of age and weighed 15 pounds.

*From the Department of Pediatrics, Kern General Hospital and Kern County Public Health Department.

Eli Lilly and Company generously furnished Actidione for two years through Dr. R. Rice of the Research Department.

On July 26, 1948 the patient was brought to the pediatric clinic because the mother said "his right shoulder was out of place." The orthopedic department failed to confirm this, but noted a small mass at the distal end of the right clavicle. August 20, 1948, the x-ray department reported an area of rarefaction in the right frontal region of the skull, and a cystic area at the distal end of the right clavicle. The chest showed a hazy infiltration in both lung fields and a bilateral hilar adenopathy. The x-ray diagnosis was coccidioides osseous and pulmonary—tuberculous to be ruled out and metastatic lesion, such as neuroblastoma, to be considered. Coccidioidal spherules were recovered from the cystic area which was a granuloma breaking down. The culture was also positive for *C. immitis*. At one year of age an x-ray survey showed cystic changes in the first and fifth metacarpal bones and a large cystic lesion in the head of the right tibia. Thus the diagnosis of disseminated coccidioides was made. Spherules were seen from all the broken down draining granulomas which also showed positive cultures. August 30, 1948, a new cystic lesion developed in the left elbow, and in the left mandible followed by drainage. The child had periodic pain in the lumbar area. X-ray study failed to show any lesions there. September 10, 1948 the patient had a hemoglobin of 13.1 gram and 84 per cent. The white blood count was 15,400 with a differential of 75 per cent lymphocytes, 1 per cent eosinophiles and 24 per cent segmenters. The urine was negative. The sedimentation rate was 25 mm. with a hematocrit of 37 per cent. A four plus coccidioidin skin test was obtained. The complement fixation test for coccidioides was done at the University of California. On September 3, 1948 it was reported four plus through 1:32 dilution. He was started on Actidione¹ therapy—10 mgm. tramuscularly three times a week and worked up to higher doses. An ointment was also made of 60 mgm. in one ounce of aquaphor for the open lesions. A syrup of Actidione, containing 5 mgm. per dram, was also taken. A survey on March 13, 1950 showed that all the draining lesions were dried up and the cystic osseous lesions were becoming relatively smaller.

May 6, 1949 the titer had risen to a four plus in 1:64 and plus minus in 1:128 dilution. March 24, 1950 the complement fixation was four plus in 1:64 and later dropped to a one plus in 1:32 dilution with all the lower dilutions four plus. Dr. C. E.

Smith concluded that the gradual but definite fall in titer continued in line with clinical improvement. The child had one year of therapy with Actidione and was clinically improved. This case² was mentioned once as just starting therapy.

The patient was not seen again until three months before this present hospital admission. He complained then of pain in his legs. He was again admitted to the hospital and signed out by his parents in three hours.

The physical examination revealed a very poorly nourished and moderately well developed Mexican lad who appeared to be in a terminal condition. His head was enlarged with frontal bossing. The suture lines of the cranium were separated as noted by palpation. The ears were normal. The eyes had bilateral proptosis with the upper lids covering over one-half of the eyeballs. The left pupil was contracted. The right pupil reacted to light. The pharynx was negative. The chest revealed prominent ribs with the interspaces sunken. The lungs were negative to physical examination. The heart was also negative to physical examination. The liver and spleen were not palpable on abdominal examination. The extremities and anus were negative. The skin was dry with poor turgor. There were many healed cicatrices from former draining coccidioidal granulomas in the left mandible, left clavicle, left groin, elbow and popliteal areas. The neurological examination revealed that the patient would answer questions but slowly. He responded to pin pricking, heat, cold and pressure applications. A negative Brudzinski and Kernig signs were noted. All other reflexes were hypoactive. A two plus nuchal rigidity was noted. Laboratory tests: First strength coccidioidin and Mantoux were negative. The hemoglobin was 4.4 grams and 26 per cent. The red blood count was 1,570,000 and a color index of .83. The white count was 7,000 and had 58 per cent lymphocytes, 10 per cent stab. cells and 32 per cent segmenters. The sedimentation rate was 14 mm. with a hematocrit of 16 per cent. A signal tap showed 6 cells and all lymphocytes. It was clear. The pressure was not increased. The sugar was 56 mgm. per cent and the protein was 575 mgm. per cent. The blood complement fixation for coccidioides was $4 + 1:2$, $3 + 1:4$, $\pm 1:8$. The spinal fluid culture was negative for *C. immitis* and other organisms. A bone marrow puncture was done. It was reported that "all cell series are present, but

decreased in number. There are many basket cells. Throughout there are clumps of cells which appear to be different from the usual hematopoietic cells. They have uniform chromatin in large nuclei with blue cytoplasm for the most part. There are some mitotic figures and some nucleoli present. It is impossible to tell what these cells are. There is no evidence of coccidioidomycosis."

X-ray report April 3, 1951: Re-examination of chest when compared with those taken Nov. 28, 1951 shows some cardiac enlargement with prominence of the left ventricle. There is some increase in the hilar bronchovascular markings. There is questionable pathology in both apices but this is not definite. There is spotty demineralization in all the visualized osseous structures, including ribs, cervical spine, shoulder girdles. The abdomen showed some distention of all the bowel loops from stomach to descending colon. The skull showed considerable enlargement of the cranial vault, and considerable separation of the cranial sutures, particularly in the region of the sagittal sutures and lamboidal sutures indicating increased intracranial pressure. There is soft tissue swelling in the scalp and an opaque catheter is seen entering the cranial vault. There is increase in the convolutional markings. There is no evidence of erosion of the posterior clinoids.

The patient was given small blood transfusions and an indwelling polyethylene catheter was inserted into the ventricles for relief of pressure.

The last week before the child expired ethyl vanillate³ was given orally. The demise occurred April 10, 1952. He was then four years and eight months of age.

AUTOPSY REPORT*

Body: An extremely emaciated, hydrocephalic, light colored, male Mexican child, appearing approximately the stated age of 4 years. The skull is exceedingly soft and contains extensive hemorrhagic raised areas. The dura on the left side shows thickened hemorrhagic tissue between the dura and the skull.

Cranial Cavity: The skull cap has been previously described. The brain weighs 1080 grams and shows very little meningeal reaction. There is a mass at the base of the skull just posterior to the foramen magnum measuring about 7 x 5 x 4 cms. between

*PM 85, 1952 by Dr. Robert W. Huntington, Jr.

the dura and the skull. On cut section it is homogeneous and pale and is thought to represent coccidioidal granuloma. There are also hemorrhagic retro-orbital masses about 2 cms. in diameter.

Thoracic Cavity: There are pale granulomatous masses along side the vertebral column in the thorax.

Abdominal Cavity: There are large retroperitoneal lymphnodes and there is a large mass surrounding the right kidney. The large mass surrounding the right kidney, previously described, also surrounds the adrenals.

Heart: The heart weighs 70 grams and the valve measurements are as follows: Mitral 6 cms., tricuspid 9 cms., pulmonic 4.5 cms., aortic 4.5 cms., left ventricle 8 cms., right ventricle 4 cms. The valves and the mural endocardium show nothing of note.

Lungs: The right lung weighs 100 grams, and the left lung weighs 90 grams. Both are pale and show no obvious masses on palpation. The tracheobronchial lymphnodes are small.

Liver: The liver weighs 450 grams. There are small pale nodules beneath the diaphragm. The texture of the organ appears unremarkable.

Spleen: The spleen weighs 40 grams and shows nothing of note.

Intestine and Mesentery: The peritoneal surfaces are smooth and glistening. The intestines show nothing of note.

Stomach and Duodenum: The stomach is somewhat distended and contains a considerable amount of greenish material, mostly liquid.

Pancreas: The pancreas is studded with granulomatous nodules.

Adrenals: The left adrenal is grossly unremarkable. The right adrenal, as previously noted, is buried in granulomatous tissue.

Kidney: The left kidney weighs 90 grams. The right kidney, with attached granulomatous material which cannot be dissected free, weighs 200 grams. Pelves and ureters are not dilated. The left kidney is pale. Its surface is smooth and the capsule strips with ease. The corticomedullary relationship appears normal. On cut section the right kidney shows the hyperplastic mass previously described; encroaches upon the cortex and upon the pelvis.

Lymphnodes: The retroperitoneal, periaortic and iliac nodes have already been described.

Arteries and Veins: No atherosclerosis or other significant changes.

Neck Organs: Normal to palpation.

Cranial Cavity: Previously described.

Provisional Anatomical Diagnosis: Disseminated coccidioidomycosis. Note: Both in gross appearance and in distribution this process, evidently coccidioidal, strongly resembles neuroblastoma.

Formalin Fixed Brain: Examination of the fixed brain shows congestion and perhaps hemorrhage beneath the arachnoid of the frontal lobes. No significant focal lesions are found within the brain substance.

MICROSCOPIC

Kidney Mass: Blocks show kidney and adrenal surrounded and infiltrated by tumor composed of small dark cells. In some areas there is a papillary arrangement about connective tissue stalks, reminiscent of that of ependymal tumors.

Left Adrenal: Small tumor nodule.

Lymph Nodes: Infiltrated with tumor. No intact granulomata are noted, but areas of calcification are present.

Spinal Cord: Not remarkable.

Liver: Not remarkable.

Spleen: Not remarkable.

Dural Nodule: Tumor.

Lung: Atelectasis.

Myocardium: Not remarkable.

Pancreas: A lobule is infiltrated by tumor.

Note: An organism recovered on post-mortem culture was thought to be *C. immitis*. Subsequent study showed this identification to be incorrect, since conidospores were found. The organism died out before final identification could be made.

BACTERIOLOGY

Abdominal lymphnodes, dura: TB smears; no acid fast observed. TB culture: No acid fast observed. Coccidioides; Wet mount; no spherules observed. Guinea pig inoculation: Negative. Final Diagnosis: Sympathicoblastoma.

COMMENT

As a rule when a patient has disseminated coccidioides with multiple draining granulomas and osteolytic lesions the prognosis

is very poor. This is especially so if the patient is of the Mexican, Filipino or colored races. Fifty per cent of the disseminated cases in this group mentioned will die. We are never absolutely certain of the clinical recovery of the remaining 50 per cent. It has been our experience that some of this class on post-mortem examination show an active gland which gives a positive culture *C. immitis*. We had repeatedly recovered from many of this patient's draining granulomas the spherules of *C. immitis*, and confirmed by cultures. We had been using Actidione, an irradiated streptomyces gresius preparation, for two years, and the clinical results had not justified its continued use. It did however seem to prolong some of the coccidioidal meningitis cases. We exhibited the clinical results at the 1950 American Medical Association meeting in San Francisco. We also stated then that the drugs would not be released to the profession because the results were poor.

Actidione was shown by Whiffen¹ to inhibit *C. immitis* in vitro in strengths greater than 1000 micrograms per milliliter. That concentration was impossible to obtain in humans because the toxicity was manifested in very low doses. Our patient had a total of 5 grams in a period of one year. Actidione caused vomiting in 10 to 30 minutes after an intramuscular injection. Small doses were given, such as 10 mgm. thrice weekly, then 15, and finally 20 mgm. intramuscularly.

There have been some cases in which the patient's complement fixation will be in the severely disseminated range and after years will drop to a low dilution. Yet we are not absolutely sure that this type of case is completely healed. That is precisely why this case is scientifically and clinically interesting. The granulomatous findings on the post-mortem examination certainly would have one think it was disseminated coccidioides based on past findings. Nevertheless, the microscopic study showed a generalized neoplastic disease (sympathicoblastoma), sympathicoblastoma of adrenal gland with metastasis, and all cultures for *C. immitis* were negative. The absolute certainty of no coccidioidomycotic infection in the body of this case will give investigators in this field encouragement that it can be cured. Could Actidione be a carcinogenic agent in this case? It is not likely. Many of our present antibiotics come from streptomyces and they have not been incriminated in their use.

The orbital involvement should have alerted the examiner to the fact that it is a common metastatic area for neuroblastomas, yet periorbital granulomas are seen many times in disseminated coccidioides. The bone marrow puncture nearly gave us the ante-mortem diagnosis as "the clumps of cells which appear to be different from the usual hematopoietic cells" which was reported could have been speculative for a neurogenic tumor. Whether this neurogenic tumor had been there for over three years or not is only a conjecture.

SUMMARY

A severe disseminated coccidioidomycosis case is reported as completely cured with an antibiotic called Actidione. The drug was clinically tried for two years with poor results in many other cases of disseminated coccidioides. The crux of this case is that the necropsy has given encouragement for complete cures in this disease, but a non-toxic drug must be found to do it.

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ETIOLOGY OF RETROLENTAL FIBROPLASIA. (Schweizerische medizinische Wochenschrift, Basal, 82: 381, April 12, 1952.) A single case of retrolental fibroplasia was discovered among 570 prematurely born infants who weighed less than 2,000 gm. at birth. A search for etiological factors revealed that the recent introduction of a new type of incubator and the use of high concentrations of oxygen probably played a part in development of retrolental fibroplasia. They suggest two possible causes: (1) the unphysiological administration of oxygen may cause the eye lesions or (2) although the prematurely born infant may become adapted to the oversupply of oxygen, damage occurs when the baby is removed from the high oxygen atmosphere. The authors feel that oxygen must be used cautiously in prematurely born infants.—*Journal A.M.A.*

CLINICAL REVIEW

In order to encourage the writing of clinical articles by recent graduates or senior medical students, the ARCHIVES will publish monthly at least one such paper from the classes of Doctor Reuel A. Benson, New York Medical College, New York, and Doctor Philip Moen Stimson, Cornell Medical School, New York. Other interested medical schools are cordially invited to submit student papers for consideration.

GYNECOLOGIC PROBLEMS OF INFANCY AND CHILDHOOD*

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The field of gynecology can be divided into five periods as follows: 1. Infancy and Childhood. 2. Puberty. 3. Maturity. 4. Menopause. 5. Senility.

Much can be found in the various texts and periodicals concerning the last four periods but little has been written regarding the gynecologic problems of infancy and childhood. This is a subject of concern to both the gynecologist and the pediatrician. Not only must one know the various conditions occurring in this period but one must also be familiar with the normal pelvic anatomy and methods of examination of the immature female child.

DIFFERENCES OF PELVIC ANATOMY IN THE IMMATURE FEMALE

The pelvic anatomy of the young child differs considerably from that of the adult woman. This is a subject not only neglected in clinical teaching but one which even the anatomy texts cover only very superficially.

The External Genitalia. The mons pubis of the child is somewhat flatter and is devoid of pubic hair. In comparison with the vulva of the adult, that of the child shows relative underdevelopment and less recession and the labia minora are more conspicuous than the labia majora. The clitoris is situated beneath the anterior labial fold and before maturity appears larger and more prominent. At birth the clitoris is relatively larger than the other vulvar structures. In actuality this structure in the young

*Submitted as partial fulfillment of the requirements of the course in Senior Pediatrics at the New York Medical College, Flower and Fifth Avenue Hospitals, New York.

child may approximate in size that of the adult. Thus there may be little change in the size of the clitoris from birth to puberty. The hymen of the child is a protruding or cufflike structure while in the adult it is a flat occlusive diaphragm. Usually several openings or a cryptiform hymen is present but a completely imperforate hymen is not a rarity. The size of the average hymenal orifice varies little if at all from infancy to puberty. Accounting for the infrequency of bartholinitis in immature girls is the presence of only rudimentary Bartholin glands.

The vagina in infancy and childhood is a thin, underdeveloped structure. A few days after delivery extensive desquamation of the vaginal epithelium occurs and it is transformed into a rather thin membrane which persists until puberty. Due to the absence of significant amounts of estrogenic hormones there is little keratinization of this epithelium. The vaginal pH which is high at birth soon falls to between seven and eight where it remains until puberty. The small vagina of the infant is actually only a potential cavity with very closely approximated, fluted and cryptiform walls. The lower part of the vagina shows characteristic longitudinal plicae while the upper part shows more circular pleats.

Exposure and identity of the vaginal cervix is often quite difficult. Usually the vaginal cervix is flattened at its end and presents a pin-point orifice. The cervical canal is rounded, tubular and almost aglandular being lined with low columnar or cuboidal epithelium.

The pelvic floor of the child is firm and muscular.

The Internal Genitalia. Outstanding factors are the small size and lack of intricate differentiation of the pelvic organs of the child. The uterine size remains small until just a few months prior to puberty. The cervix of the immature uterus constitutes about two-thirds of the length of the entire organ. The immature uterus stands almost straight in the pelvic inlet and is situated higher in the pelvis of the child than in the adult. The endometrium for several weeks after birth may show the influence of maternal estrogenic effects. This gradually disappears and until just prior to puberty the endometrial glands show simple tubular structures. Thus the endometrium of the immature uterus is a fixed or stationary tissue. In childhood there is a relatively meager vascular and lymphatic supply to the uterus. The cervix until

almost puberty retains its infantile characteristics and as previously stated the canal is almost aglandular. The fallopian tubes, which are more convoluted in infancy and childhood, straighten considerably as adulthood approaches. They also show increases in both length and diameter at this time. The tubes of the child are quite small structures with rather simple mucosal pattern.

At birth the ovaries which are long, slender and flattened still lie at the pelvic brim. Afterwards the ovaries and uterus gradually attain their pelvic positions. In infancy the ovaries are not over half the size of ovaries in the active reproductive period. The external surface of the ovary of the young child is smooth; follicles begin to be visible at about nine to ten years of age. Simple ovarian follicle cysts in young, who do not show evidence of any precocious sexual development, are not uncommon. In general, the ovarian size seems to progress more in relation to the age of the child up to adolescence than does the uterine size. By eight to nine years of age the germinal epithelium of the ovary has been converted from tall columnar type of cells to a thin layer of endothelium-like cells. Since estrogen can generally be demonstrated in urine and blood between eight and eleven years, the ovary probably under pituitary influence becomes an active gland of internal secretion about this time.

METHODS OF EXAMINATION

As in any examination the first essential is to obtain as adequate a history as is possible. In pediatrics of course there are certain essential differences in this procedure. It must be remembered that particularly in regard to conditions related to the pelvic organs the history as obtained from the mother is apt to be colored by her own emotional reactions. Likewise the timing of complaints may be very inaccurate, e.g., a vaginal discharge may be present for a considerable length of time before noted by the mother. The importance of gaining the child's confidence should not be underestimated, since even a fairly young child may be able to render information not obtainable from the parent. Particularly in the older child often careful inquiry without the parent present may elicit facts of importance in diagnosis.

In any examination of children, instruments should be kept out of sight until it is necessary to use them. Before undertaking

any procedures the child should be told what to expect if she is old enough to understand. The inspection of the external genitalia should never be neglected in any routine physical examination. Usually the lithotomy position is best for careful inspection. The legs of the small child may be held by an assistant, while the older child can utilize the stirrups of the regular examining table. The vulva is spread apart thus allowing full visualization of the clitoris, fourchet and hymen. Any discharge present is noted as to amount, color, consistency and odor. Prior to any examination of the genitalia the parts should be thoroughly cleansed with warm soap and water. If the child is made to cough, strain or even cry the hymen will be seen to protrude forward. To identify the caliber of the hymenal orifice a fine metal probe may be utilized. The physician must be careful not to attempt to enter an imperforate hymen or a minute hymenal orifice since the hymen is very sensitive and the child's cooperation will be lost.

Obtaining Vaginal Smears. A small caliber glass catheter proves very useful in this procedure. The catheter is first inserted into warm normal saline solution and saline allowed to remain in the end of the catheter. The catheter is then gently inserted into the vaginal vault and moved gently to and fro, thus picking up sufficient vaginal secretion to inoculate the retained saline. The gross characteristics of the discharge are recorded and, if smears are not definitely diagnostic, appropriate culture media must be inoculated with the discharge.

Rectal Examination. As in all examinations of the child, gentleness is very important. If properly evaluated the findings by rectal examination in small children may be actually more exact than those obtained by vaginal examination. Rectal examination is often of great value in elucidation of foreign bodies in the vagina. Hymenal, vaginal and rectal abnormalities, pelvic masses, areas of tenderness as well as bulging of the cul-de-sac or rectal wall may be detected. Uterine abnormalities in the child are only palpable if gross pathological alterations are present. In the very young child it may be necessary to utilize the small finger for rectal examination.

Digital Vaginal Examination. In girls over ten years of age, vaginal examination with the index finger is often accomplished with surprising ease. For complete relaxation general anesthesia

may be necessary. As in rectal examination any of the following may be elucidated: hymenal, vaginal or rectal abnormalities; pelvic masses or tenderness; any bulging of the cul-de-sac or rectal wall. As in the adult, combined abdominal-pelvic examination is of value, although it is often much more difficult to detect adnexal and uterine abnormalities in the child.

Rectovaginal Examination. Combined examination may prove very useful; particularly is the combined rectal-digital and vaginal instrumental examination of value in the removal of a foreign body from the vagina without vaginoscopy. The course of the instrument is guided and followed by the rectal finger. This method of course should not be utilized if the type of foreign body is unknown or if the foreign body is a sharp object.

Vaginoscopic Examination. When such examination is indicated it can often be best performed under general anesthesia. A valuable instrument for this procedure is a small size cystoscope which can easily be passed into the vagina. A small bivalve vaginal speculum or nasal speculum can be useful in the older child.

Only special examinations related to gynecologic conditions have been discussed here but as in any other condition a complete physical examination with evaluation of the entire child is important. It is usually best to complete the routine physical, including abdominal palpation, before one conducts any special examinations. The small child under about six years of age attaches no more significance to examination and treatment of conditions about the genitalia than to examination and treatment of other parts. The older child's reaction frequently reflects her psychic environment and the physician should show sympathetic understanding and attempt to gain the confidence and cooperation of the child in the management of both the physical and emotional aspects.

TYPES OF GYNECOLOGIC PROBLEMS ENCOUNTERED IN INFANCY AND CHILDHOOD

These problems can be classified as follows: 1. Inflammations. 2. Trauma. 3. Anomalies. 4. Tumors. 5. Endocrine disturbances.

Inflammations. Primary infection of the immature vagina is fairly frequent. The endocervix is relatively immune to infection and extension of infection to the uterus and tubes in childhood is very rare.

Procedures necessary in the differential diagnosis of the type of vaginitis include: 1. Detailed history. 2. Complete physical examination with special reference to the amount, color, odor and consistency of the vaginal discharge. 3. Smear of discharge. 4. Culture of discharge—unless smear definitely diagnostic. 5. Determination of pH of discharge—use of nitrazine paper.

The four types of vaginitis seen in pediatric practice are: gonorrheal vaginitis, nonspecific vaginitis, foreign body type vaginitis and premenstrual vaginorrhea.

Gonorrheal Vaginitis. This type of vaginitis is seen less commonly today than before the advent of penicillin therapy. It is often very difficult to obtain the source of the infection. In the young child it is usually due to direct contact as in sex play, while in the older child it may be due to sexual intercourse with an infected individual. Late recurrent positive cultures are sometimes obtained from children long thought cured. Gonococcal vaginitis may occur secondarily to rectal infection. According to a study conducted by Reuel A. Benson, it seems gonorrheal vaginal infection in the immature female is almost constantly due to contact with an infected individual. In this study toilet seats used by children with active infection as well as their bed linens and clothing were meticulously cultured and seldom yielded positive results. In fact, the results of cultures of the toilet seats were so consistently negative, uninfected children were permitted to also use them and infection did not result. Usually the discharge in gonorrheal vaginitis is profuse, greenish-yellow and purulent.

The pH of the immature vagina as well as the delicate thin epithelium favors the growth of the gonococcus. Thus in treatment the rationale behind the use of estrogenic hormone therapy is the production of epithelial thickening and the shifting of the pH to that of the adult vagina. The only disadvantage to this form of therapy is a temporary enlargement of the breasts in a few cases. Quick results can be obtained in most cases by the use of estrogenic vaginal suppositories. Today, penicillin has proven very efficacious in most cases without the use of any local therapy.

Gonococcal infection in childhood may not be as innocuous as many believe since the following complications have been observed in a fair percentage of cases: urethritis, proctitis and purulent conjunctivitis.

Nonspecific Vaginitis. This includes all those vaginal inflammations due to poor hygiene, lack of cleanliness, improper clothing, poor nutrition, chronic skin diseases, pinworm infestation, masturbation or chronic illness. In most cases the discharge is thin, watery and light yellow in color. Treatment is aimed at discovery and removal of the underlying cause. Usually chemotherapy and estrogenic therapy prove ineffective. It should be remembered that many infections, not demonstrating the gonococcus even on repeated cultures, may be due to this organism. *Trichomonas vaginalis* is infrequent in the immature vaginal tract. Also fungus and yeast infestations are very rare. In such conditions the diagnosis and treatment would be similar to that used in the adult.

Foreign-body Vaginitis. This should be suspected in any case with persistent foul smelling, bloody or brownish vaginal discharge. Rectal examination, roentgenograms of the pelvic area and vaginoscopic examination may be useful in diagnosis. The history in such cases is seldom helpful. Treatment consists of removal of the foreign body and psychotherapy to prevent recurrences.

Premenstrual Vaginorrhea. The discharge consists of large quantities of desquamated epithelial cells. This is not uncommon and usually there is no demonstrable pathology. It is usually associated with hyperestrinism of adolescence and from the standpoint of cleanliness may be very bothersome. The parent and the child should be assured that this is a normal physiological condition and no treatment is necessary.

Trauma. Trauma, particularly to the vulva and adjacent structures, is not uncommon in childhood. There are two types of trauma to the external genitals: contusions in the perineal region, and impalements. Impalements result from a fall on a sharp object, such as in climbing over a fence. Although such injuries may bleed profusely, due to the extreme vascularity of the area, they seldom bleed long and subsequent infection is rare. Edema develops rapidly and is apt to be very extensive. Hematomas also form readily in this region and it may sometimes be necessary to evacuate large hematomas. The prompt application of cold packs and pressure to the area with the child in horizontal position will aid in prevention of edema and hematoma formation. The healing and restoration of normal contour in cases of vulvar lesions is very rapid and as stated above infection is rare.

The physician handling cases of attempted rape should be well acquainted with the medicolegal aspects involved which are beyond the scope of this paper.

Anomalies of the Female Generative Tract. Although anomalies are common unless they involve the external genitalia they are frequently not detected during infancy or childhood. Often it is not until the beginning of marital relations or the occurrence of pregnancy that an anomaly of the generative tract is discovered. This discussion will only concern those types of anomalies that are apt to be discovered before puberty.

Hermaphroditism. This term applies to the union of both sexes in one individual. A true hermaphrodite has both types of sexual glands—testis and ovary. A pseudohermaphrodite has only one type of sexual gland, either testis or ovary. In both types the accessory sexual glands are generally confused. The organs are apt to be rudimentary or incompletely developed. Often in pseudohermaphroditism, the external genitalia are predominantly of the opposite sex from the gonads present. Such is a frequent cause for incorrect diagnosis. Therefore, prior to any operative surgery on the external genitalia, exploratory laparotomy is a prerequisite to definitely determine the true sex of the individual. Male pseudohermaphroditism is more common than the female type. Gynecologic surgery has much to offer these individuals. Fortunately true hermaphroditism is extremely rare.

Aplasia or Absence of Organs. Except for very rare cloacal defects these are seldom discovered in childhood.

Developmental Inhibitions. Those due to incomplete union of the müllerian ducts, etc., are rarely noted before adulthood. An imperforate hymen is the commonest type of external vaginal atresia. This may sometimes be noted on routine examination, although often it is not discovered until onset of menarche and subsequent development of hematocolpos. An occluded or restricted hymenal orifice may favor vaginal stasis and maintain intravaginal infection. It would be well if obstetricians and pediatricians would note the vaginal introitus of the newborn female child. A restricted orifice may be dilated while in cases of imperforate hymen hymenectomy is indicated although many believe such procedures should not be performed until later in life. Certainly before any attempt is made to penetrate or dilate the

hymen a rectal examination should be done to rule out a congenital absence of the vagina. Any child, who is approaching the age at which menses may be expected and who exhibits cyclic pelvic pain, characteristic developmental changes and no flow, should be examined for possibility of an occluded hymen. Usually, if vagina is absent, there is no cervix or uterus present. The external genitalia and vaginal orifice in such cases may appear normal. This is sometimes discovered by an observant mother or nurse. Of all the labial defects probably the simplest is agglutination of the proximal edges of the labia minora. Treatment consists of a simple median incision of the adhesion.

Uterine Prolapse. Complete uterine prolapse has been reported in the newborn infant. It is a condition not infrequently associated with spina bifida.

Ovarian Hernia. This may be congenital or acquired. The ovary on one or both sides may be palpated in the inguinal canal. The ovarian pedicle in such cases may become twisted and the organ strangulated.

Circumcision of Female Child. Although this may be a subject not usually considered under anomalies of the generative tract some mention should be made in regard to the occasional indications for this procedure. The clitoris may be deeply buried under a redundant and adherent foreskin. Rarely circumcision will be indicated when a visibly adherent foreskin becomes associated with persistent congestion, irritation and pruritus and the child's attention is becoming focused on the genital area.

Tumors and Other Major Pelvic Pathology. Children with pelvic disease often present a clinical picture of either an acute abdomen or chronic intra-abdominal disease. Occasionally there may be no symptoms other than an abdominal mass or endocrine disturbances. Since the pediatrician usually is the first to see these children he must be alert to the possibilities of pelvic disease in children. The routine performance of rectal examination in any child with abdominal complaints should be emphasized. Preferably such examination should be made with child under light sedation. It is also important to remember that ovarian tumors may be pedunculated and are often abdominal rather than pelvic.

Physiologic ovarian cysts in the adult rarely require any treatment or cause complications, while the reverse is true in the child

where weight of cyst often causes torsion not only of pedicle but often also of adjacent tube.

The most common benign ovarian neoplasm causing symptoms in childhood is the dermoid cyst. Such cysts are sometimes bilateral. Often there are no symptoms until the pedicle becomes twisted.

Malignant ovarian tumors are predominantly sarcomatous as are also other malignant neoplasms of childhood. Dysgerminoma is not an uncommon ovarian tumor in early life. Although this tumor undoubtedly belongs in the malignant class, there is marked variation in the degree of malignancy. Clinical outcome appears to be determined by such factors as presence of bilateral lesions, whether or not the growth is well encapsulated and whether or not the tumor has twisted on its pedicle. The treatment, as with other ovarian malignancies, is surgical but the extent of the surgery must be determined for each individual case. If tumor is of infiltrating type, radical removal of the pelvic organs is indicated and this is followed by deep x-ray therapy. Postoperative radiation of course is not employed in cases treated conservatively. The functioning ovarian tumors will be discussed under endocrine disturbances of infancy and childhood.

Symptoms of Pelvic Pathology. The child may complain of dull, aching abdominal pain or present the typical picture of an acute abdomen with sudden onset of severe pain, etc. Nausea and vomiting may occur due to severe pain or sudden peritoneal irritation. There is frequent reflex vomiting in children. Low grade fever is often associated with malignancies but usually is absent with benign ovarian cysts unless complicated by torsion or rupture. Many children show marked febrile reactions with any condition and which are not commensurate with the severity of the disease. Thus the degree of fever cannot be considered as pathognomonic in differential diagnosis of pelvic conditions. Often the child presenting the picture of an acute abdomen shows marked leukocytosis and the differential diagnosis between pelvic conditions, appendicitis or diverticulitis, etc., becomes impossible to make preoperatively.

Examination of Child Suspected of Pelvic Pathology. Here again the importance of a carefully obtained, detailed history must be mentioned. In general examination of the child the occurrence of secondary sex characteristics suggestive of ovarian, pituitary or

adrenal disorder is noted. Usually for abdominal examination the prone position will allow better demonstration of the rebound mechanisms. A nervous child frequently requires mild sedation before examination. It must be remembered that tumors of pelvic origin are often abdominal in location and palpation of upper abdominal masses does not exclude the possibility of such as pedunculated ovarian neoplasms. If an abdominal mass is palpated a history of the rate of growth is very important. Marked abdominal ascites as with malignancy may make palpation of mass impossible without aspiration. It is questionable whether aspiration should be attempted in such cases since surgical exploration will be indicated regardless of other findings.

Vaginal examination should not be neglected if rectal findings are indefinite. In either type of examination an empty bladder is a prerequisite. The presence of any amount of vaginal bleeding is important since this may indicate the presence of a functioning ovarian tumor or precocious puberty. In performing pelvic examination of the immature child it is necessary to be familiar with the differential normal findings as compared to the adult woman. Between ten and twelve years of age the growth of the pelvic viscera is accelerated and the findings on examination more closely resemble those of maturity.

Additional Diagnostic Aids. 1. X-ray, the chief value of which lies in revelation of calcification within the mass, almost definitely labeling the mass as a teratoma but not differentiating between benign cystic and malignant solid types. In the diagnosis of feminizing tumors x-rays of the long bones may be used as an adjunct.

2. Cystoscopy and pyelograms may be necessary to rule out congenital anomalies of urinary tract and renal tumors. Neoplasms of the immature female genital tract are not unlike those found in the adult, although sarcomas are more common than carcinomas. Occasional cases have been reported of adenocarcinoma of ovary and of uterine cervix in young children. The treatment of such neoplasms, whether benign or malignant, is surgical usually, with cases of malignancy often post-operative irradiation. Each case must, of course, be evaluated individually in regards to the extensiveness of surgery.

Pelvic Peritonitis. The diagnosis of pelvic inflammatory disease

in the child can very seldom be confirmed. Except when extension from intra-abdominal pathology is obvious, the origin of pelvic infection in young female children is attributed to the lower genital tract. The causative organisms in order of frequency are: pneumococcus, gonococcus, colon bacillus, streptococcus and staphylococcus. Very rarely the tubercle bacillus is involved. Salpingitis per se is rarely noted and then only in older girls.

The differential diagnosis of pelvic peritonitis in the young child may be very difficult since it is important to determine if the inflammation is secondary to an inflamed appendix or if it is a true primary peritonitis. As the treatment of one is surgical and of the other conservative, a sincere attempt to differentiate must be made. Since appendicitis in the immature girl has higher incidence of occurrence than primary peritonitis, usually, if in doubt, exploration is performed. In the child surgical drainage of pelvic abscess is usually done abdominally rather than vaginally. Colpotomy is indicated only in case of an obvious fluctuating and pointing abscess of the cul-de-sac. In any inflammatory condition of the pelvis, extensive antibiotic therapy should be instituted. Also attention must be given to the proper fluid and electrolyte balance of these children. These items are adequately covered in pediatric textbooks.

Endocrine Disturbances of Infancy and Childhood. Symptoms referable to the endocrine system are common during this period. Genital hemorrhage other than during menstruation may result from inflammation, foreign bodies, injury, neoplasms, asphyxia at birth or be a manifestation of a hemorrhagic disease. In the newborn period, due to the influence of maternal hormones, there may be a bloody discharge noted from the vagina. Precocious menstruation, in which flow occurs at more or less regular intervals, is usually accompanied by other signs of sexual and somatic precocity. In some cases menses continue for a period and then cease, while in others continue into adulthood. Precocious menstruation may be a symptom of tumor or adrenal, pineal body or ovary or be due to hypersecretion of anterior lobe of the pituitary. Cases of precocious menstruation, associated with fibrous dysplasia of bone and pigmentation of the skin, have been described by Albright. In all cases the important factor is to find the underlying cause and then apply the appropriate treatment.

Gonadal Sexual Precocity. This is usually due to neoplasm. The most common feminizing ovarian tumor which occurs in childhood is the granulosa cell tumor. This tumor in the child causes precocious development of the reproductive organs and rapid maturity of the secondary sex characteristics. Most cases reported of the granulosa cell tumor have been unilateral. The treatment of such tumors is surgical, but there exists considerable debate regarding the extent of the surgery. Some advocate conservative surgery in the younger age group with frequent follow-up examinations, others advise radical treatment regardless of the age of the patient since it is a malignant tumor and recurrences are not uncommon. The degree of malignancy varies widely in these tumors. Another tumor which occurs in childhood and produces similar symptomatology to the granulosa cell tumor is the thecoma. Chorionepithelioma of the ovary is rare, but its possibility should not be overlooked. It is analogous to the chorionepitheliomas of the testicle and hence is in no way related to uterine chorionepithelioma except for its morphologic similarity. These also are usually unilateral and may be responsible for sexual precocity in the child.

There have recently been reports of a considerable number of functioning ovarian tumors occurring in childhood. Although extremely rare, a masculinizing tumor which has been reported in girls of older age group is the arrhenoblastoma. After removal of the tumor regression of the masculinizing symptoms, although not always complete, is striking. Since such tumors appear to have a relatively low degree of malignancy, conservative surgery with frequent follow-up examinations seems to be justified. As with other ovarian neoplasms in childhood probably each case should be individually evaluated.

Ovarian Agenesis. Dwarfism associated with congenital abnormality of the ovaries is often also associated with other congenital abnormalities. Clinical features of such cases include: mature facial features, normal skeletal proportions and infantile sexual development. There is an associated high incidence of hypertension for which no explanation can be found. These cases show high follicle-stimulating hormone excretion and low 17-ketosteroid excretion. There is also delay in epiphyseal union. It has been suggested that ovarian agenesis is due to a defect of

germ plasm, causing failure of primordial germ cells to develop or persist in the development of the ovaries. Other disturbances of endocrine function are most notable after the onset of puberty.

SUMMARY

A discussion has been given concerning the more frequent gynecologic problems of infancy and childhood. Methods of diagnosis and the anatomical differences in the genital tract of the immature female have been presented. No attempt has been made to cover the detailed pathology of the various conditions.

CONCLUSIONS

1. Gynecologic conditions are not uncommon during infancy and childhood.
2. In order to properly evaluate such conditions the physician must be familiar with the normal anatomical pelvic findings of the immature female.
3. Since type of therapy may have considerable effect upon the later life of the girl, any child with signs or symptoms of anomaly or disease of the generative tract should be referred to a competent gynecologist for consultation.

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DEPARTMENT OF ABSTRACTS

FISHER, O. D. AND WHITFIELD, C. R.: TERRAMYCIN IN THE TREATMENT OF PNEUMONIA IN CHILDREN. (British Medical Journal, 4789:864, Oct. 18, 1952).

A clinical trial of pneumonia in 50 children using terramycin or a "standard treatment" of penicillin and sulphonamide, has been made. The two groups are considered to be comparable and the results of treatment in each group assessed. It is suggested that penicillin and sulphonamide remain the most satisfactory treatment for pneumonia in childhood.

AUTHORS' SUMMARY.

HSIA, D. Y.-Y.; ALLEN, F. H.; GELLIS, S. S. AND DIAMOND, L. K.: ERYTHROBLASTOSIS FETALIS. VIII. STUDIES OF SERUM BILIRUBIN IN RELATION TO KERNICTERUS. (New England Journal of Medicine, 247:668, Oct. 10, 1952).

Kernicterus is likely to occur in babies with serum bilirubin levels above 30 mg. per 100 cc. and unlikely to occur when serum bilirubin remains below 20 mg. per 100 cc. Therefore, although it has not been proved that bilirubin is the actual cause of brain damage, tests of serum bilirubin in babies with erythroblastosis fetalis serve as extremely valuable guides to treatment. By exchange transfusion, repeated if necessary, the serum bilirubin can be kept at relatively low levels, and kernicterus can be prevented.

AUTHORS' SUMMARY.

AREY, J. B.: CANCER IN CHILDHOOD. (Medical Clinics of North America, 36:1797, Nov. 1952).

Cancer, including leukemia and Hodgkin's disease, is now one of the leading causes of death from disease between the ages of one and 14 years. Leukemia, the most common fatal type of cancer in childhood, still offers a hopeless prognosis; however, even in this disease, significant but temporary improvement may be expected in many patients after therapy. Rates of cure in a number of other types of cancer in early life prove that the defeatist attitude, commonly encountered among those responsible for the treatment of such neoplasms, is not justified. There is

considerable variation between the clinical and pathologic aspects of neoplasms in early life, and those observed in adult life. Observation of the dictum that "every solid mass in an infant or child should be regarded as a malignant neoplasm until proved otherwise" should result in earlier diagnosis and improved rates of cure.

AUTHOR'S SUMMARY.

McDONALD, P. R.: RETROLENTAL FIBROPLASIA. (Medical Clinics of North America, 36:1579, Nov. 1952).

Retrolental fibroplasia is an ocular disease affecting premature infants. It is the greatest cause of blindness in the preschool child today. Approximately 50 per cent of all infants weighing less than three pounds at birth show evidence of the acute phase of the disease. This consists in dilatation and tortuosity of the retinal vessels and peripheral graying and elevation of the retina. Regression occurs in about 60 per cent of these cases, so that only 15 to 20 per cent of premature infants exhibit the cicatricial phase. This consists in a partial or complete retinal detachment. This may form a complete membrane behind the lens. The anterior chamber is shallow, posterior synechia develop, and secondary glaucoma may ensue. The disease is primarily confined to the retinal vessels. There is marked capillary budding and endothelial proliferation. Hemorrhage occurs into the vitreous, and secondary contracture causes a retinal detachment. Nothing is known concerning the etiology. At one time it was thought to be due to excessive use of certain water-miscible vitamins or iron. This has since been disproved. Vitamin E, 50 mg. three times a day, is believed by some to reduce the severity of the cicatricial phase. ACTH and cortisone are no longer considered to be of any value in treatment or prophylaxis, and their use is not recommended. The socio-economic status of the patient plays no role in this disease. The only factor that we are certain of is that it is a hazard of prematurity. Every effort should be made to avoid premature births.

AUTHOR'S SUMMARY.

BOOK REVIEWS

POLIOMYELITIS. PAPERS AND DISCUSSIONS PRESENTED AT THE SECOND INTERNATIONAL POLIOMYELITIS CONFERENCE. Cloth. Pp. 555. Philadelphia: J. B. Lippincott Co., 1952.

This book contains the papers, discussions and exhibits that were presented at the Second International Poliomyelitis Conference at the University of Copenhagen in September 1951. A book of this type is always of interest and value because it brings together under one cover the ideas and thoughts of many men who have a common interest. Of the many fine discussions presented the ones I thought particularly interesting were: Virus and Host Factors Determining the Nature and Severity of Lesions and of Clinical Manifestations by D. Bodian; Differential Diagnosis in Paralytic Poliomyelitis by R. Debré and S. Thieffry; Laboratory Aspects of the Differential Diagnosis in Acute Poliomyelitis by J. E. Smadel and C. V. Adair; Management of Respiratory Insufficiency by J. L. Wilson (is particularly good) and Factors Which Influence the Clinical Course of Poliomyelitis by W. R. Russell. Most of the discussions are brief and cogent.

MICHAEL A. BRESCIA, M.D.

MODERN MEDICATION OF THE EAR, NOSE AND THROAT. By Noah D. Fabricant, M.D., M.S. Cloth. Illustrated. Pp. 245. Price \$5.75. New York: Grune & Stratton, 1951.

This book has been on the whole most disappointing and has nothing to commend it to the pediatrician. The author seems to try hard being scientific and appears to "talk down" to his reader. The author makes frequent use of the parenthesis without sufficient cause and begs the intelligence of his readers by parenthetically noting that the tympanic membrane is the ear drum and acute rhinitis the common cold.

MICHAEL A. BRESCIA, M.D.

YOUR CHILD CAN BE HAPPY IN BED. By Cornelia Stratton Parker. Illustrated by Heda Teitcher. Cloth. Pp. 275. Price \$2.95. New York: Thomas Y. Crowell Co., 1952.

This book is well written and offers many ideas for doing things

to entertain children when confined to bed and incidently teach them arts and crafts. It covers many crafts using paper, clay, paints, etc. Many of the materials recommended are easily available and not too expensive. There are many worthwhile suggestions to help entertain the sick child either with games or crafts. The first chapter dealing with the "bed box" is a most helpful hint on how to put away "odds and ends" to the day when they will be needed to keep the sick and convalescent child busy in bed.

LAVERNE E. BRESCIA, R.N.

TREATMENT OF HEMOPHILIA BY PLASMA INJECTIONS. (Semaine des Hôpitaux de Paris, 28: 380, Feb. 6, 1952). The hemostatic value of a clot depends on the quantity of thrombin formed during the clotting process rather than on clotting time. Clot structure in hemophilia is characterized by loose meshes and fragile fibrin filaments; after injection of frozen plasma, the clot appears normal, with numerous centers of coagulation, thick fibrin filaments, and compact meshes. Comparatively large quantities of plasma are needed to secure a normal serum prothrombin level; repeated injections are cumulative in their effect, so that a normal serum prothrombin level can be maintained in a hemophilic person for several days. Serum prothrombin, however, returns to its initial level within 24 hours after a single plasma injection; the effect of plasma on clotting time is more lasting, continuing for about 48 hours. Frozen plasma injections are simple and efficacious and may be given instead of whole blood transfusions whenever the antihemophilic factor alone is needed, that is, when hemorrhage is not accompanied by hypovolemia or pronounced anemia. They may also be used prophylactically when the clotting time falls below a safe level. Difficulties due to lability of the antihemophilic factor may be avoided by preparation and freezing of the plasma within three hours after blood is obtained. Thawing should be rapid but not abrupt. Plasma may be given drop by drop at the rate of 100 cc. every 15 minutes. Its hemostatic action is as spectacular as that of whole blood; hemorrhages are arrested, and dental operations can be carried out under the protection of daily plasma injections.—*Journal A.M.A.*

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